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The impact of severe mental illness on lung cancer mortality of lung cancer patients in Finland in 1990-2013: a register-based cohort study

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Abstract

Background

While the link between severe mental illness (SMI) and elevated cancer mortality is well established, few studies have examined lung cancer survival and SMI in detail. Our study compared cancer-specific mortality in lung cancer patients with and without a history of SMI, and whether mortality differences could be explained by cancer stage at presentation, comorbidity or differences in cancer treatment.

Methods

We identified patients with their first lung cancer diagnosis in 1990-2013 from the Finnish Cancer Registry, their preceding hospital admissions due to SMI from the Hospital Discharge Register and deaths from the Causes of Death statistics. Competing risk analyses were used to estimate hazard ratios (HR) for the impact of SMI on mortality.

Results

Out of the 37,852 lung cancer cases, 12% had a history of SMI. Cancer-specific mortality differences were found between patient groups in some cancer types after controlling for stage at representation and treatment. Men with history of psychosis had excess mortality risk (HR 1.24, 1.06-1.45) in squamous cell carcinoma. Similar excess risk was found among women with psychosis in small-cell carcinoma (HR=1.76, 1.41-2.19) and in squamous cell carcinoma (HR=1.67, 1.26-2.20) and among women with mood disorders in adenocarcinoma (HR=1.37, 1.08-1.74). Patient group differences in HRs in five-year mortality did not markedly change from the 1990s.

Conclusions

We found elevated cancer-specific mortality among persons with a history of SMI. Collaboration between patients, mental health care professionals, and oncological teams is needed to reduce the mortality gap between cancer patients with and without SMI.

Abstract: 248 words (Eur J Cancer: 250 + list of keywords)

Manuscript: 2558 words (Eur J Cancer: 2500)

Keywords

lung cancer, mental illness, survival, health services research, register-based study

Highlights

3-5 bullet points (maximum 85 characters, including spaces, per bullet point).

- We studied the effect of mental illness on cancer-specific mortality in lung cancer
- We found elevated cancer-specific mortality in patients with mental illness history
- The mortality gap persisted after controlling for cancer stage and treatment
- Patients' psychiatric team should be included in cancer care to enhance outcomes
- Smoking cessation interventions should be integral component of lung cancer care

Introduction

Lung cancer remains the most common cancer world-wide, the most common cancer among men and the leading cause of cancer-related death.[1, 2] In Finland, lung cancer ranked the third most common cancer during our study period among men, and seventh among women.[3] In 2015, the age-standardized incidence of lung cancer in Finland was 26.2 for men and 22.6 for women per 100,000. The five-year relative survival was 11% among men, and 18% among women.[3] Smoking is the ultimate risk factor of lung cancer with 80-90% of incident cases attributed to it.[4, 5] Its effect is lower in adenocarcinoma.[6] Risk factors for poor prognosis include advanced age, comorbidity, smoking, late stage at diagnosis and non-optimal treatment.[7]

There is mounting evidence of elevated all-cause mortality among people with severe mental illness (SMI).[8] Additionally, in a meta-analysis, Catts and colleagues[9] observed increased lung cancer incidence among patients with schizophrenia which, however, disappeared after adjusting for smoking prevalence.

Most studies have found increased all-cause[2, 8, 10-17] and cancer-specific mortality[18, 19] among lung cancer patients with SMI, while some have reported difference in neither.[16, 20, 21] These conflicting results may reflect differences in study populations, designs and definitions. Most studies examine lung cancer as a single mortality category and do not allow for closer look at comorbidity, cancer stage or treatment. Further, most studies do not distinguish between morphological types of lung cancer and focus exclusively on schizophrenia.

The aim of our study was to examine whether cancer-specific mortality in lung cancer patients with a history of SMI was higher than in lung cancer patients without SMI, and whether mortality differences could be explained by comorbidity, cancer stage at presentation, or differences in cancer treatment. We also examined potential change in these outcomes during the study period.

Materials and methods

The study population

Data on patients with their first lung cancer diagnosis in 1990-2013 were obtained from the Finnish Cancer Registry containing nationwide data on virtually all cancers diagnosed in Finland since 1953.[22] We examined the data back until 1953 to exclude patients with any prior cancer diagnoses. Lung cancer was defined based on ICD-O-3 topography codes C33 and C34 as cancer

located in trachea, bronchus or lung. Cancers defined morphologically as lymphoma (ICD-O-3 morphology codes M959-973, n=221) were excluded. Cancers first diagnosed in autopsy (n=8,329) were also excluded. Lung cancers first diagnosed in autopsy represented 19% of original data among men and 14% among women. Among men, cases first diagnosed in autopsy varied from 19% in those without history of SMI to 21% in persons with non-affective psychotic disorder (NAPD). Differences in proportions found in autopsy were somewhat larger among women. Patients were allocated into four groups on the basis of morphology: 1) adenocarcinoma (ICD-O-3 codes M814-838), 2) small cell lung carcinoma (SCLC, M8041-8045), 3) squamous-cell carcinoma (SCC, M805-808), and 4) other.

Data on SMI in 1969-2013 were identified from the Hospital Discharge Register and individually linked to the cancer data. Hospital admissions due to SMI were only taken into account if they were recorded as main diagnoses and occurred at least one year before cancer diagnosis to exclude incident psychiatric disorders linked to cancer.[23] Information concerning history of SMI was classified into four main categories; non-affective psychotic disorder (NAPD, ICD-10 codes F20, F22-29 and corresponding ICD-8 and ICD-9 codes), substance use disorder (SUD, ICD-10 codes F10-19), mood disorder (MD, ICD-10 codes F30-33 and F38-39) and no SMI. Due to the long natural course of SMI, patients remained in the SMI population until the end of the follow-up. If patients had admissions in several SMI categories, they were classified hierarchically into NAPD, SUD, and MD groups.

Causes of death for the cohort were obtained from the Causes of Death statistics of Statistics Finland until the end of 2014 from which the coding experts of the Cancer Registry had further determined whether they were cancer-specific by examining the cause of death records together with other data on the cancer in question. Ethical approval for the study was received from the Research Ethics Committee of the National Institute for Health and Welfare.

Covariates

Cancer stage at the time of diagnosis was classified into three groups; 1) localized, 2) metastasized (regional or distant), and 3) unknown. Cancer treatment was classified into six categories; 1) surgical treatment, 2) radiotherapy, 3) chemotherapy, 4) surgical treatment and chemotherapy, 5) radiotherapy and chemotherapy, and 6) other or no treatment or unknown.

A modified Charlson's comorbidity index[24] was calculated for each patient using the Hospital Discharge Register records to mark the burden of comorbidity. Several diseases (congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatic disease, peptic ulcer disease, liver disease, diabetes with or without chronic complications, hemiplegia or paraplegia, and renal disease) within five years preceding cancer diagnosis were used in the calculation.

Age at lung cancer diagnosis was stratified as under 45 years, subsequent 5-year groups, and those 85 years or older. Other variates included the year of cancer diagnosis and sex. Cause-specific death was the main outcome event and deaths of other causes were considered as competing outcome events. Patients were followed from the date of cancer diagnosis until the end of 2014 or earlier death or emigration. Those alive at the end of follow-up were censored at emigration or on 31 December 2014.

Statistical methods

We cross-tabulated the distributions of covariates by SMI group. Pearson's χ^2 test was used to test differences in cancer type distribution among patient groups. We then calculated Kaplan-Meier estimates to describe survival differences between patient groups. In graphs, Kaplan-Meier curves were cut at 10 years of follow-up. Analyses were done separately for men and women, and by type of lung cancer.

Proportional subdistribution hazards regression models with other causes of death as competing risk events were conducted in three steps to assess differences in case-specific mortality in patient groups and to study the impact of covariates on patient group differences during the whole study period.[25, 26] In the first step, we estimated hazard ratios for patient groups adjusting for age, year of cancer diagnosis since 1990, cancer type and Charlson's comorbidity index as well as interaction of cancer type and patient group. In the second step, we further adjusted for cancer stage at presentation. In the third step, cancer treatment was added to the model. In each model, we calculated contrasts for differences for patient groups in lung cancer categories. We used generalized R^2 to assess how well each set of covariates predicted mortality.[27]

In order to study if differences between patient groups altered during the study period, we adjusted competing risk models with 5-year follow-up in three cancer incidence periods (1990-

1994, 1997-2001 and 2004-2008) to ensure equivalent potential follow-up. We used age group, incidence period, cancer type, Charlson's comorbidity index, cancer stage at presentation, and cancer treatment as covariates and calculated second and third degree interaction terms for patient group, cancer type and incidence period. Interaction terms were examined to assess possible changes in time in mortality between patient groups in lung cancer categories.

For sensitivity analysis, we conducted similar models for cause-specific mortality with Cox regression models. The R statistical software version 3.5.1 was used in statistical analyses.[28]

Results

In our study data, there were 37,852 incident lung cancer cases diagnosed between 1990 and 2013 of whom 27,557 were men. 35,299 patients died (including 31,900 case-fatalities) during the total follow-up time of 60,177 person-years. Table 1 shows basic background characteristics of the study population. Among men, 13% of lung cancer patients had a history of SMI with SUD being the largest group. Among women, 10% of the lung cancer population had a history of SMI with NAPD as the largest group. Average duration of SMI until cancer incidence varied from 15.9 years among men with MD to 24.9 years among men with NAPD. The proportion of adenocarcinoma was higher among female cancer patients, whereas SCC was higher among male cancer patients. Cancer type distributions differed in patient groups among men and women (both $p<0.001$).

Kaplan-Meier curves (Figure 1) showed lower survival in NAPD group for SCLC among women, and for SCC among both men and women. Survival was also lower in MD group for adenocarcinoma among women.

Table 2 presents the hazard ratios (HR) of cancer-specific mortality with other causes of death as competing risk event in patient groups by sex and cancer type in three steps with those without SMI as reference category. Overall, our results showed that while stage at presentation (Model II) and cancer treatment (Model III) did explain a fair share of variation in mortality as indicated by the generalized R^2 values, some statistically significant differences remained between patient groups. Among men, patients with NAPD had HR of 1.24 in SCC in Model III. Among women, similar and even larger relative risks of lung cancer mortality were found among patients with NAPD with HR of 1.76 in SCLC and 1.67 in SCC. The MD group among women with adenocarcinoma had an elevated risk (HR=1.37) in model III. In 'other' type of lung cancer, NAPD and SUD groups

had elevated HRs among men (1.19 and 1.18) as well as NAPD group among women (1.18) after adjusting for all covariates.

HRs for SMI groups from models estimated in three periods for 5-year follow-up did not change markedly in any of the cancer types.

Sensitivity analyses produced largely similar results. In full models, while NAPD group in SCLC had similar risk to the results presented, it was, however, statistically significant among men whereas statistical significance of difference between MD group and those without history of SMI among women in adenocarcinoma disappeared.

Discussion

Overview of main findings

This registry based study covering years 1990-2014 found elevated cancer-specific mortality risk among lung cancer patients with a history of non-affective psychotic disorder (NAPD) and substance use disorder (SUD) compared to lung cancer patients without severe mental illness (SMI) history even after controlling for stage at presentation, comorbidity and cancer treatment. More specifically, we found elevated risk of cancer-specific mortality among both male and female patients with a history of NAPD in SCC, among female patients with a history of NAPD in SCC and among Female patients with mood disorders (MD) in adenocarcinoma. According to our results, differences in cancer-specific mortality did not change during the study period between persons with or without SMI history.

Earlier evidence of increased lung cancer mortality among lung cancer patients with SMI is mixed.[12, 17, 19] Our result of elevated cancer-specific mortality among lung cancer patients with NAPD differs from that of Lawrence et al.[21] who did not find elevated case-fatality among lung cancer patients in psychiatric patient population compared to general population in a study in Western Australia in 1982-1995. Comorbidity and stage at presentation were not adjusted for in their study.

Delayed diagnosis and lower likelihood of receiving adequate cancer care among psychiatric patients along with higher incidence of adverse treatment outcomes have been suggested to be possible reasons behind differences in outcomes.[12, 20, 29, 30] In line with our results, a recent

study from the U.S. found that poor survival among non-SCLC patients with pre-existing SMI was not explained by delay in diagnosis or inadequate cancer treatment.[11] Our results also remained after controlling for stage at presentation and cancer treatment. While there were patient group differences in cancer treatment in our study, they are likely to be related to differences in the distribution of cancer types between patient groups.

As for patients with mood disorders, concurrent depression has been linked to poor lung cancer survival and it has been suggested that patients with depression choose not to initiate or continue treatments.[14, 15] However, evidence concerning depression is mixed.[15] In our study, the differences between SMI groups were more prominent among women. This is likely to be partly explained by larger prevalence of competing causes of death among men. Also, there is evidence of better survival among women with SCLC in general population.[31]

Smoking has been found to be more prevalent among patients with NAPD and SUD compared to those with MD or no history of SMI[32], and smoking cessation has been linked to improved prognosis of lung cancer[33]. We did not have information on smoking or smoking cessation interventions, but it is possible that high rates of smoking contributed to the excess mortality in patients with SMI. Smoking cessation interventions are effective and well tolerated in patients with SMI[34-36], and they should be an integral component of lung cancer treatment.

Methodological considerations

Strengths of our study include a nationwide cohort enabling a 24-year follow-up. The Finnish Cancer Registry has been reported to have close to 100% coverage of incident cancer cases with the accuracy of the records found to be good.[22] It made it possible for us to distinguish between histological types of lung cancer, stages of cancer at presentation and cancer treatment for the whole study period. We were able to identify histories of severe mental illnesses and information on comorbidities since 1969 from the Hospital Discharge Register, the coverage and overall accuracy of which has been considered good.[37] Our data enabled us to distinguish between cancer-specific and other causes of death. The Finnish Causes of Death statistics have been reported to be reliable and valid by international standards.[38] Additionally, the cause-of-death information among lung cancer patients has been revised with records in the Finnish Cancer Registry enhancing the quality of our mortality data compared to most studies and enabling us to

use the competing risk approach to correctly estimate marginal probability of a cancer-specific death in the presence of competing events.

We were not able to study cancer treatment adherence, communication between oncological teams and patients, co-operation with patients' primary care or psychiatric team or health behavior among SMI patients, which have also been linked to poorer lung cancer prognosis.[11, 14, 18, 30, 39] Further, comorbidity which has been linked to outcomes of lung cancer[11, 40] may have been insufficiently controlled for with the Charlson's comorbidity index used in the current study. Neither did we have data on health behavior of lung cancer patients, particularly on smoking status. The cancer data contained quite large proportions of patients with unknown stage or treatment. Furthermore, the historical long-term coding nomenclatures of stage and treatment in the Cancer Registry records did not enable us to classify these factors into more precise categories that may be optimal in modern clinical terminology. In our study, lung cancer patients with cancer type 'other' with a history of NAPD and SUD had a higher lung cancer mortality risk. As the proportion of 'other' type was higher among SMI patients, that may reflect worse accuracy in the diagnostic process among them. We were unable to include the duration of SMI in competing risk models. Our data only contained diagnoses for mental illness treated in a hospital setting, overlooking less severe cases, especially SUD and MD.[41] This reduces generalizability of our results.

Conclusions

We found persistent excess cancer-specific mortality in lung cancer patients with a history of severe mental illness. Further studies are needed for understanding all factors contributing to mortality differences including physical comorbidity, help-seeking behavior, and adherence to treatment recommendations as well as problems concerning stigmatisation and poorer cancer care. Collaboration between the patients, their outpatient mental health care team, oncological team and primary care professionals is needed throughout the cancer episode to guarantee optimal treatment and increase survival among this patient group.

Role of the Funding Source

This study was partly funded by the Cancer Society of Finland. The Society had no involvement in design, data collection, findings or decision to publish.

Conflicts of interest

The authors report no conflicts of interest that would have biased the work.

Data statement

Due to data protection legislation in Finland individual-level data on the study subjects cannot be released.

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Figure legend

Figure 1. Kaplan-Meier curves for the distribution of cancer-specific survival by severe mental illness category in four types of lung cancer among Finnish men and women diagnosed with lung cancer in 1990-2013.

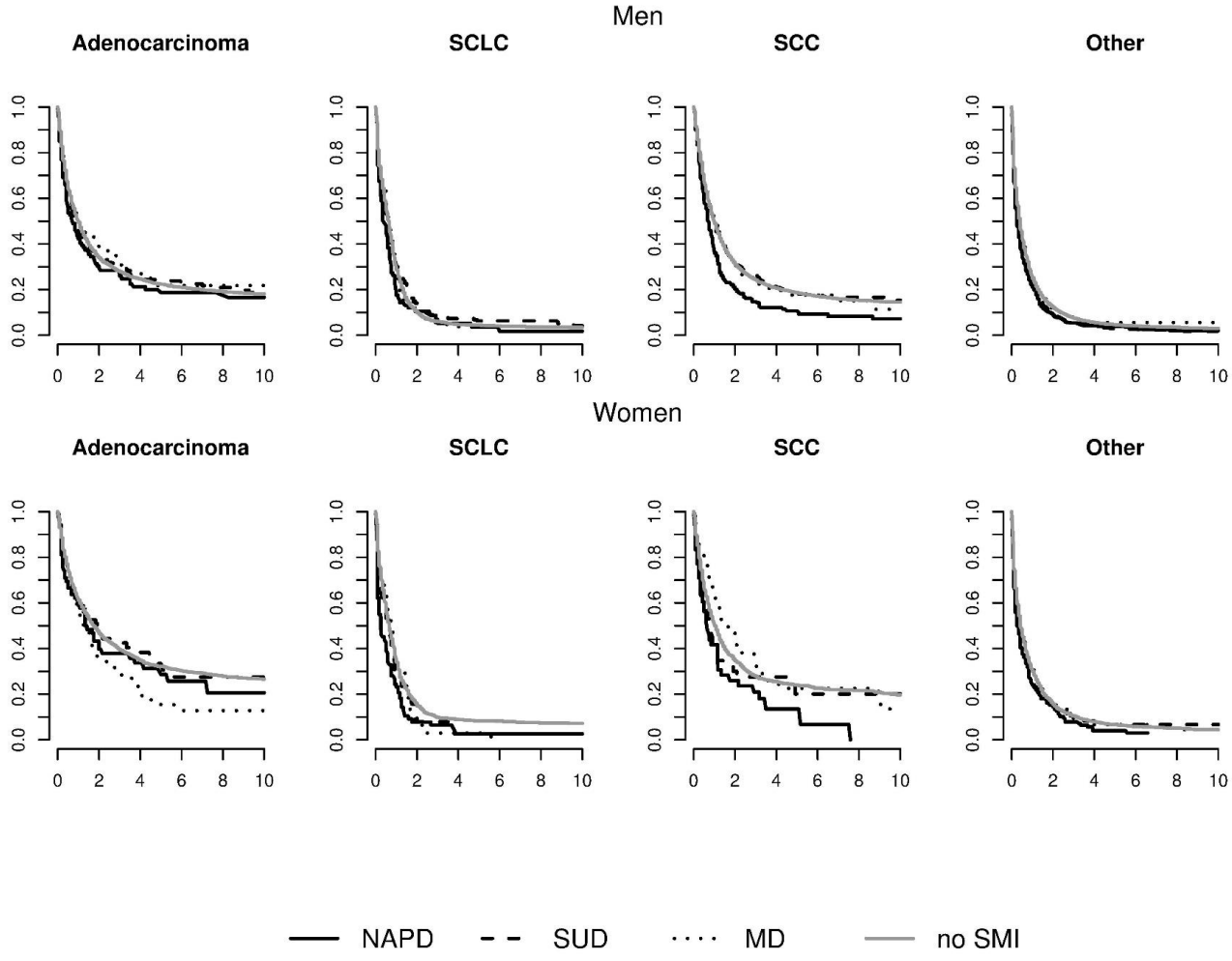

Table 1. Baseline characteristics of population with first lung cancer in 1990-2013 in Finland, by sex and SMI category.

Variable	category	Men				Women			
		NAPD	SUD	MD	no SMI	NAPD	SUD	MD	no SMI
Cases	N	955	2222	452	23928	405	288	318	9284
	(%)	(3)	(8)	(2)	(87)	(4)	(3)	(3)	(90)
Cancer type	adenocarcinoma	12	16	14	18	17	25	21	30
(%)	small cell lung carcinoma	10	13	13	13	20	16	14	13
	squamous-cell carcinoma	26	25	24	25	12	17	14	12
	other	52	46	50	45	51	43	51	45
Age at presentation	(mean)	64.5	65.5	68.6	69.4	65.8	64.1	69.0	69.5
Charlson's index	(mean)	0.19	0.20	0.22	0.22	0.15	0.14	0.17	0.17
Stage at presentation	local	13	15	17	15	11	18	14	15
(%)	metastisized	62	63	63	64	64	60	60	63
	unknown	25	22	21	21	25	22	26	22
Treatment	operative	9	11	10	12	6	13	8	12
(%)	operative + chemotherapy	1	3	4	3	3	3	5	4
	chemotherapy	7	11	11	11	11	12	9	13
	radiotherapy	24	19	19	22	16	18	16	17
	chemotherapy + radiotherapy	7	11	11	13	10	13	16	14
	other / none / unknown	51	45	44	39	54	41	47	41

NAPD, non-affective psychotic disorder; SUD, substance use disorder; MD, mood disorder; SMI, severe mental illness.

Table 2. Effect of history of severe mental illness to lung cancer mortality among Finnish men and women with lung cancer by cancer type in 1990-2013; hazard ratios (HR) and their 95% confidence intervals (CI).

		Men						Women					
		Model I		Model II		Model III		Model I		Model II		Model III	
		HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Adenocarcinoma	NAPD	1.13	0.90-1.42	1.14	0.91-1.42	1.08	0.83-1.41	1.19	0.88-1.60	1.21	0.91-1.61	1.08	0.81-1.42
	SUD	1.10	0.97-1.26	1.14	0.98-1.31	1.14	0.98-1.32	1.07	0.78-1.45	1.33	0.95-1.85	1.28	0.91-1.82
	MD	0.89	0.66-1.22	0.95	0.68-1.32	1.04	0.76-1.42	1.42	1.12-1.80	1.35	1.05-1.73	1.37	1.08-1.74
	no SMI	1.00		1.00		1.00		1.00		1.00		1.00	
Small cell lung carcinoma	NAPD	1.26	0.98-1.61	1.28	0.99-1.65	1.25	0.96-1.62	1.82	1.43-2.31	1.83	1.44-2.32	1.76	1.41-2.19
	SUD	1.01	0.88-1.15	1.04	0.91-1.18	1.02	0.89-1.18	1.13	0.78-1.64	1.14	0.78-1.66	1.13	0.74-1.72
	MD	1.12	0.87-1.43	1.17	0.94-1.47	1.08	0.81-1.44	1.01	0.76-1.35	0.95	0.71-1.29	0.98	0.74-1.30
	no SMI	1.00		1.00		1.00		1.00		1.00		1.00	
Squamous-cell carcinoma	NAPD	1.49	1.29-1.71	1.50	1.30-1.73	1.24	1.06-1.45	1.69	1.23-2.33	1.78	1.34-2.36	1.67	1.26-2.20
	SUD	1.09	0.98-1.20	1.14	1.03-1.26	1.06	0.95-1.17	1.24	0.87-1.77	1.33	0.94-1.89	1.34	0.95-1.88
	MD	1.06	0.85-1.32	1.11	0.89-1.39	1.10	0.88-1.37	0.93	0.70-1.25	1.05	0.78-1.42	1.01	0.73-1.40
	no SMI	1.00		1.00		1.00		1.00		1.00		1.00	
Other	NAPD	1.27	1.15-1.40	1.31	1.18-1.44	1.19	1.07-1.32	1.19	1.02-1.40	1.25	1.06-1.46	1.18	1.00-1.38
	SUD	1.23	1.15-1.32	1.26	1.18-1.35	1.18	1.11-1.27	1.12	0.92-1.37	1.18	0.96-1.44	1.13	0.91-1.39
	MD	0.99	0.86-1.15	1.00	0.87-1.16	0.96	0.83-1.12	0.99	0.82-1.19	1.03	0.86-1.22	1.02	0.86-1.22
	no SMI	1.00		1.00		1.00		1.00		1.00		1.00	
	Generalized R^2	*0.0829*		*0.1771*		*0.2308*		*0.1232*		*0.2365*		*0.2774*	

NAPD, non-affective psychotic disorder; SUD, substance use disorder; MD, mood disorder; SMI, severe mental illness.
Model I: adjusting for age group, year of incidence and Charlson's comorbidity index
Model II: Model I + cancer stage at presentation
Model III: Model II + cancer treatment